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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/912,947 | 07/25/2001 | Bjorn Dahlback | INL-036DV | 7730 |

22832 7590 09/01/2006

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 09/01/2006

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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/912,947
Filing Date: July 25, 2001
Appellant(s): DAHLBACK, BJORN

Fangli Chen
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 06/14/2006 appealing from the Office action mailed 12/27/2005.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

In particular, Appellants brief identifies the following interference proceedings for the parent of the present application, US Serial No. 08/500917: Patent Interference No. 105,235; Patent Interference No. 105, 268; and Patent Interference No. 105, 269.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

**NEW GROUND(S) OF REJECTION**

Claims 46, 53-55, 64-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is considered a new ground of rejection because the examiner has applied additional references to the rejection.

Since the statutory basis for the new grounds of rejection is the same as the statutory basis for the ground of rejection in the final office action on the merits, the appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

de Visser, M. C. H. et al. "The HR2 Haplotype of Factor V:Effects on Factor V levels, Normalized Activated Protein C Sensititivity Ratios and the Risk of Venous Thrombosis", Thromb. Haemost. Vol 83 (2000), pp. 577-82.

Pennisi, E. "A Closer Look at SNPs Suggests Difficulties", Science, vol. 281 (18 September 1998), pp. 1787-1789.

Bertina, R. "Genetic Approach to Thrombophilia" Thromb Haemost. vol. 86 (2001), pp. 92-103.

Price, D.T. "Factor V Leiden Mutation and the Risks for Thromboembolic Disease: A Clinical Perspective", Ann. Intern. Med. vol. 127 (1997), pp. 895-903.

WO 99/52942 Blumenfield 10-1999

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***New Grounds of Rejections***

***Claim Rejections - 35 USC § 112, 1st ¶***

Claims 46, 53-55, 64-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the Invention**

The invention is drawn to methods for predicting a risk of developing thrombosis and/or APC resistance caused by a gene mutation via screening of samples for the occurrence of Factor V gene mutations or abnormal presence or absence of a nucleic acid fragment or sequence in Factor V gene that give rise to the expression of a mutated Factor V/Va molecule. Thus, the nature of the invention requires the knowledge of a mutation or abnormal presence or absence of a nucleic acid fragment or sequence in the Factor V gene which is associated with a risk of developing thrombosis and/or APC resistance.

**Breadth of the Claims**

Claim 46 is drawn to a method for determining a risk of developing thrombosis and contains method steps of obtaining a sample from an individual, conducting a nucleic acid assay on the sample, determining the abnormal presence or absence of at least one nucleic acid fragment or sequence in the individual's factor V gene, comparing the individual's Factor V gene sequence to a normal Factor V gene and detecting a risk of developing thrombosis based on individuals Factor V gene. The implication of the claim is that the determination of risk is based on an abnormality of the patient's gene sequence, though the claim does not give the structure of the abnormality. Claim 53 depends from claim 46 and requires the genes are compared via sequencing. Claim 64 depends from claim 53 and requires that the sequencing assay uses reagents specific for Factor V gene. Claim 65 depends from claim 64 and requires detecting an abnormal nucleotide sequence in Factor V gene.

Claim 54 is drawn to a method for identifying a presence of a Factor V gene mutation associated with APC-resistance in an individual at risk for APC resistance by obtaining a sample from an individual, conducting a nucleic acid assay on the sample, determining the presence of the Factor V gene mutation associated with APC resistance in the individual's factor V gene by comparing the individual's Factor V gene sequence to a normal Factor V gene sequences. Claim 55 depend from claim 54.

Thus, the claims encompass screening methods which detect any mutation and abnormal presence or absence of any nucleic acid fragment or sequence within the Factor V gene in an individual, with some claims requiring the expression of a mutated factor V/Va molecule (detecting abnormal presence or absence of a nucleic acid fragment of factor V gene), association with APC resistance, and an association of developing a risk of thrombosis.

**Teachings of the Specification, Working examples**

The specification teaches at ¶ 0081 that a "neutral polymorphism" in the Factor V gene has linkage with inherited APC resistance. The specification does not give the structure of the polymorphism, i.e. where, within the gene, the polymorphism is located or what base change occurs, nor does the specification disclose any polymorphism or mutation within the Factor V gene that result in the expression of a mutated factor V/Va molecule.

The specification does not give any guidance on how to predictably correlate any abnormal presence or absence of factor V gene with the type of thrombosis in an individual nor does the specification teach a study that predictably correlates a mutation of Factor V gene associated with APC resistance. The specification does not teach an association with factor V gene mutation or abnormal presence or absence of Factor V gene to any type of thrombosis.

Based on the guidance in the specification, it is unclear if the absence or presence of Factor V gene would yield a positive or negative risk of thrombosis. The specification is merely prophetic that the detection of a neutral polymorphism in the Factor V gene is linked to inherited APC resistance.

The guidance provided in the specification amounts to an invitation for the skilled artisan to try and follow the disclosed specification to test an individual for abnormal presence or absence of Factor V gene or mutation of Factor V gene for any thrombosis disorder or APC resistance and determine if the presence of the particular mutation or abnormal presence or absence of nucleic acid fragment or sequence of Factor V gene is responsible for the susceptibility of a risk of any thrombosis disorder or disease and the specification does not teach which mutation or abnormal nucleic acid fragment to test.

There are no working examples in the specification which exemplify an embodiment of the claimed methods.

**State of the Prior Art**

The prior art does not provide any genetic variations within the Factor V gene that are associated with thrombosis or APC resistance.

**Level of Unpredictability**

There is a large body of knowledge in the art related to polymorphisms in general, and their association with diseases or disease states. Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states

or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). In some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

At the time of filing, the prior art does not teach or provide any evidence of a mutation in the human Factor V gene and its association with thrombosis, however post filing art teaches the unpredictability of determining any mutation in the human Factor V gene and its association with thrombosis. Bertina et al. (Thromb. Haemost. 2001 86:92-103) teach that there is still a lack of information on several genetic factors contributing to the risk of venous thrombosis. Bertina et al. teach that the degree to which alleles present in Factor V gene will influence APC sensitivity ratio is largely dependent on the precise formula of laboratory test (see page 92, 1st column, 1st and 2nd full paragraph). Bertina et al. teach that two mutations present in Factor V gene are not associated with either APC resistance or increase in thrombosis risk (see table 2). Bertina et al. teach that factor V Leiden mutation (arg506) is a risk factor for deep-vein thrombosis, cerebral vein thrombosis, superficial vein thrombosis, and portal vein thrombosis but not for primary pulmonary embolism and retinal vein thrombosis (see page 97, 1st column, 1st paragraph).

Bertina et al. demonstrate that it is unpredictable to associate a mutation or abnormal presence or absence of a nucleic acid fragment or sequence of factor V gene to different types of thrombosis in an individual.

Additionally, de Visser et al. (Thromb Haemost 2000 83 :577-82) teach that the HR2 haplotype of the factor V (FV) gene was not found to be associated with an increased risk in a population based case control study for venous thrombosis (see page 580, 2nd column, 2nd full paragraph). Furthermore, de Visser et al. teach HR2 haplotype is associated with a decrease in FV levels and decrease in FV levels is not a risk factor for venous thrombosis (See pg. 581, 1st column, 1st full paragraph). de Visser et al. teach that APC resistance depends on the type of clotting test, particular reagent used, and the influence of other factors, apart from FVL that determine the APC resistance. De Visser et al. teach that the APC resistance assay reflect the ratio between the concentration of wild type FV molecule and the FV molecule in plasma and a mutation or allele associated with a reduced FV level results in an increased level of FV, leading to a more reduced normalized APC sensitivity ratio (see page 581, 2nd column, 1st paragraph). de Visser et al. teach that the mechanism which underlies the reduction of FV levels has to be further investigated (see page 581, 2nd column, 1st paragraph). de Visser demonstrate the unpredictability of determining a mutation in the Factor V gene and determining its association with an increased risk of thrombosis and APC resistance. De Visser demonstrate that APC resistance and reduction of factor V gene levels needs to be further investigated, which demonstrates the unpredictability of associating APC resistance to any factor V mutation.

Lastly, Price et al. (Ann. Intern. Med. 1997 127:895-903) teach that Factor V leiden mutation is associated with primary and recurrent venous thromboembolism but is not

associated with an increase risk for arterial thrombosis (see data synthesis, page 895). Furthermore, Price et al. teach that no association was seen between factor V Leiden mutation and thromboembolism associated with surgery, trauma or cancer (see page 898, 1st paragraph, 1st column). Price et al. teach the largest study to address the association of risk of arterial thromboembolism and factor V Leiden mutation, no significant difference in the prevalence of the factor V mutation was found between men with myocardial infarction, cerebrovascular disease, and men without cardiovascular disease. Price et al. teach that the most population based and case control studies confirm that factor V Leiden mutation is not a risk for myocardial infarction or cerebrovascular disease (see page 900, 2nd column, 2nd full paragraph). Price et al. demonstrate that even if a mutation in factor V gene is found to be associated with one type of thrombosis does not predictably correlate that this mutation will be associated with all types of thrombosis in all individuals. Both Price et al. and Bertina et al. teach the unpredictability of associating the leiden mutation, arg506 of factor V gene with thrombosis. Furthermore, Price et al. and Bertina et al. demonstrate the unpredictability of associating a mutation in the factor V gene with thrombosis because Bertina et al. contradicts the teaching by Price et al. that the leiden mutation in factor V gene is associated with venous thromboembolism. Therefore, the association of a mutation or abnormal nucleic acid fragment of the factor V gene with thrombosis is unpredictable.

The references cited above discuss the state of the art after the filing date of this application and do not identify any mutation that can predictably indicate a risk for thrombosis. The instant application fails to add to the state of the art because it does not teach any mutations or polymorphisms within the human Factor V gene. There is a disclosure that a "neutral

polymorphism" is known to exist, but without the specific nature, location and structure of the polymorphisms itself, one of skill in the art who would practice the claimed invention would be unable to do so with a reasonable expectation of success and without engaging in an undue amount of experimentation. It is highly unpredictable which nucleotides within the human Factor V gene are the polymorphic or mutated nucleotides that are associated with disease. Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate the abnormal presence or absence of nucleic acid fragment or sequence of factor V gene or mutation in factor V gene to any type of thrombosis gene, as the specification does not teach a large sample size or confidence levels greater than 95% as shown that in post filing art that a large sample size and confidence levels less than 95% are not predictive of a risk of thrombosis. The skilled artisan would have to screen multiple variants to determine if those variants are associated with a susceptibility to different types of thrombosis in all populations. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels, abnormal presence or absence of a nucleic acid fragment or sequence in factor V gene are associated with any type of thrombosis.

**Quantity of Experimentation**

The quantity of experimentation necessary to practice the claimed invention is quite high, and would involve the screening and analysis of the Factor V gene from hundreds of patients to identify any putative polymorphisms and mutations within the gene and to establish a relationship between these and the recited phenotypes. Given the lack of guidance in the specification with regard to the presence or absence of any abnormal nucleic acid fragment or sequence of factor V gene that would be correlative to thrombosis in individual along with the

evidence in the art with regard to predictably correlating genetic assays with diseases, and the unpredictability of associating mutations within the factor V to risk of developing thrombosis, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations to determine if in fact there was either an association between each mutation, abnormal nucleic acid fragment and sequence of factor V gene in individuals with any type of thrombosis. The results of such a study are clearly unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification with regard to lack of sample size, statistical analysis, or correlation of any mutation, abnormal nucleic acid fragment or sequence of factor V gene with any thrombosis. Post filing art, Price et al. demonstrate that even if a mutation in factor V gene is found to be associated with one type of thrombosis does not predictably correlate that this mutation will be associated with all types of thrombosis in all individuals. Additionally, De Visser demonstrate that APC resistance and reduction of factor V gene levels needs to be further investigated, which demonstrates the unpredictability of associating APC resistance to any factor V mutation.

In the instant case, it would be unpredictable as to whether or not a mutation or abnormal presence or absence in a nucleic acid fragment or sequence of factor V gene would be associated with thrombosis or APC resistance. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to take into different types of venous thrombosis, arterial thrombosis, thrombosis from secondary effects, such as surgery, cancer, trauma, as evidence by the teachings of Price et al. with regard to factor V leaden mutation and its association with risks for thromboembolic diseases. The skilled artisan would have to screen multiple population

based and case control studies to determine if mutations are associated arterial thrombosis, secondary effects, venous thrombosis, etc. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such mutations and abnormal presence or absence of nucleic acid fragments and sequences would predictably determine a risk of developing any thrombosis in any individual. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, specifically thrombosis and mutations with Factor V gene, such analysis is replete with unpredictable experimentation and is considered undue.

**Conclusion**

Considering all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention.

**(10) Response to Argument**

***A- Claim Rejections - 35 USC § 112, 1st ¶***

The appeal brief filed on June 14, 2006 traverses the rejection. Appellant's arguments have been fully considered but are not persuasive for the reasons which follow.

Appellants assert on page 5, 1st paragraph, that the examiner is relying upon examples in Pennisi et al. and WO 99/52942 to show that it is highly unpredictably as to whether a particular polymorphism marker will be associated with a particular disease. Appellants state on page 6, last paragraph, that Pennisi and WO 99/59294 relied on by the Examiner is distinguishable from the present invention. Appellants assert that numerous methods may be used to associate disease genes with disease phenotypes and state that Pennisi and WO 99/59294 use genomic polymorphisms to associate disease genes with disease phenotypes and by contract, the present

application conclusively associated factor V with thrombosis or APC resistance using biochemical and clinical data without relying on the polymorphism in the Factor V gene. However, the specification does not teach using biochemical and clinical data to associate an abnormal presence or absence of a nucleic acid fragment or sequence or mutation of factor V gene with thrombosis and APC resistance. Furthermore, the claims do not require using biochemical and clinical data to associate Factor V with thrombosis or APC resistance. The claims require detecting an abnormal presence or absence in a nucleic acid fragment or sequence of factor V and associating the abnormal presence or absence to a risk of developing thrombosis, which encompasses detecting polymorphisms and SNPs. Furthermore, the only guidance in the specification for association of factor V gene with APC resistance is the assertion that recent results have shown a neutral polymorphism (SNP) associated with APC resistance (see paragraph 81, page 18). Therefore, the conclusion that the present application conclusively associated Factor V with thrombosis or APC resistance using extensive biochemical and clinical data without relying on the polymorphism in the Factor V gene is not found persuasive based on the lack of teaching provided in the specification.

Appellants assert on page 7, 1st full paragraph that throughout the specification, Appellant provides extensive clinical and biochemical evidence leading to the conclusion that Factor V has a novel anticoagulant activity and that deficiency of such activity causes thrombosis associated with APC resistance. Appellants state that 9 different categories of biochemical evidence support the conclusion that Factor V has novel anticoagulant activity. However, the claims do not require a biochemical assay to determine that Factor V has anticoagulant activity. The claims require the association of the risk of developing thrombosis by an abnormal presence or

absence of factor V gene fragment or sequence relative to a control sample and the specification does not disclose an assay that predictably correlates determining the abnormal presence or absence of factor V gene sequence or nucleic acid fragment and its association with thrombosis. The specification merely discloses biochemical studies that associate factor V with anticoagulant activity by antibody assays. These teachings in the specification do not enable one to determine if a mutation or abnormal presence or absence in a nucleic acid fragment or sequence of factor V gene will be associated with any type of thrombosis or APC resistance.

Appellant's assert on page 8, 1st full paragraph, that the linkage of a neutral polymorphism in the Factor V gene and the expression of APC resistance disclosed on page 20, lines 8-23 of the original specification, only serves as one additional piece of evidence that corroborates with the extensive biochemical and clinical data disclosed in the specification. Appellant state that the present disclosure and claimed invention does not rely on the nature of this polymorphism to establish the association between Factor V and thrombosis/APC resistance and assert that the unpredictability in using genomic polymorphisms to associate disease genes with phenotypes does not apply to the presence disclose and claimed invention. However, the claims recite detection of a mutation in factor V gene associated with APC resistance (claim 54) and risk of developing thrombosis by detecting an abnormal presence or absence of a nucleic acid fragment or sequence (claim 46) which encompass detection of polymorphisms. Furthermore, the only guidance in the specification with regard to factor V gene association with APC resistance is the assertion of linkage of a neutral polymorphism in the Factor V gene with APC resistance. The biochemical and clinical data that appellant is relying upon in the specification are antibody assays to detect Factor V and APC activity (see page 27-32) but none

of these assays detect nucleic acid presence, much less an abnormal level of a nucleic acid sequence and correlation of the abnormal level of the nucleic acid fragment of factor V gene with thrombosis or APC resistance.

The appellants assert on page 8, last paragraph, that the knowledge of a specific mutation in the Factor V gene is not required to practice the invention as recited in claim 46. Appellants state that claim 46 only requires detecting an individual who is more likely to develop thrombosis than a normal individual and that claim 46 does not require detecting a specific mutation in an individuals Factor V gene in order to determine that the individual is more likely to develop thrombosis than a normal individual. Appellants state that detection of one abnormal sequence is more likely to have abnormal anticoagulant activity compared to normal Factor V gene. This is not found persuasive, as post filing art teaches the unpredictability of associating a mutation in factor V gene with thrombosis. Price et al. (see rejection above) demonstrate that even if a mutation in factor V gene is found to be associated with one type of thrombosis does not predictably correlate that this mutation will be associated with all types of thrombosis in all individuals. de Visser et al. teach HR2 haplotype in factor V gene is associated with a decrease in factor V levels and decrease in factor V levels is not a risk factor for venous thrombosis. Furthermore, Bertina et al. teach that two mutations present in Factor V gene are not associated with either APC resistance or increase in thrombosis risk (see table 2). Bertina et al. teach that factor V Leiden mutation is a risk factor for deep-vein thrombosis, cerebral vein thrombosis, superficial vein thrombosis, and portal vein thrombosis but not for primary pulmonary embolism and retinal vein thrombosis. Therefore, detection of one abnormal sequence is not likely to have abnormal anticoagulant activity or develop thrombosis. Furthermore, post filing art teaching that

mutations found with factor V gene are not correlative to all types of thrombosis, as the claimed invention broadly encompasses.

Appellants state on page 9, 1st full paragraph, that the present specification fully enables one of skill in the art to determine abnormal presence or absence of at least one nucleic acid fragment or sequence in an individuals factor V gene compared to a normal control. Appellants assert that one of skill in the art would readily have understood how to carry out nucleic acid assays, such as hybridization and sequencing assays to determine abnormal presence or absence of at least one nucleic acid fragment or sequence in the factor V gene. While knowledge of how to carry out nucleic acid assays, such as hybridization and sequencing to determine abnormal presence or absence of nucleic acid fragment or sequence in factor V gene is not undue experimentation, the correlation of the presence of an abnormal presence or absence of a nucleic acid fragment or sequence of factor V gene and its association with the risk of developing thrombosis is unpredictable and requires undue experimentation. As stated above, post filing art teaches the unpredictability of correlating abnormal presence of factor V gene sequences with any type of thrombosis, as the art teaches that not every abnormal sequence of factor V gene will predictably correlate a risk of developing thrombosis (see Bertina, de Visser and Price above). Appellants state on page 9, last paragraph, that there was a high level of skill in the art of Factor V gene and protein in 1993 when priority applications were filed. Appellants assert that both factor V protein sequence and cDNA sequence were known before 1993. However, disclosure of the sequence of factor V gene does not enable one to make and use the claimed invention of detecting an individual at risk of developing thrombosis by determining abnormal presence or absence of nucleic acid fragment or sequence of factor V gene. Neither the prior art nor the

specification, at the time the application was filed, teach mutations or abnormal presence or absence of nucleic acid fragment or sequence within the Factor V gene and a correlation between APC-resistance or thrombosis.

Appellants state on page 10, 1st full paragraph, that methods to detect abnormal presence or absence of a nucleic acid fragment or sequence in factor V gene were well known in the art when the application was filed. However, the claimed invention requires a method of detecting the risk of developing thrombosis by detection of abnormal presence or absence of a nucleic acid fragment or sequence in factor V gene and at the time of the invention, predictably correlating the risk of developing thrombosis with the detection of abnormal presence or absence of a nucleic acid fragment or sequence in factor V gene is not enabled and was not well known, as evidenced by the post filing art cited above.

Appellants asserts on page 10, last paragraph, continued to page 10, 1st full paragraph, that it was well within the routine skill of an ordinary artisan to determine what amino acid substitution would be silent or cause only conservative substitution and what amino acid substitutions would alter a protein's function. Although amino acid substitution, isolation, and amplification of nucleic acids are routine assays, the method of predictably correlating and determining a risk of thrombosis or APC-resistance by any mutation in Factor V gene or any abnormal presence or absence of a nucleic acid fragment or sequence of factor V is not a routine assay. As stated above, for one of skill in the art to predictably correlate any mutation in Factor V gene or any abnormal presence or absence of a nucleic acid fragment or sequence of factor V with the risk of developing thrombosis in an individual, as well as APC-resistance would require undue experimentation. The skilled artisan would have to perform an extremely large study and

include different populations to determine if in fact there is an association with "any" mutation or any abnormal presence or absence of a nucleic acid fragment or sequence of factor V in Factor V gene and thrombosis and APC-resistance. The results of such a study are clearly unpredictably, as discussed in the post filing art cited above. Given that the specification does not teach a single mutation in the Factor V gene or any abnormal presence or absence of a nucleic acid fragment or sequence of factor V and its association with thrombosis or APC resistance and coupled with the lack of guidance in the prior art at the time of the priority date with determining an association of a mutation in Factor V gene or any abnormal presence or absence of a nucleic acid fragment or sequence of factor V and any type of thrombosis or APC-resistance, the analysis of determining abnormal presence or absence of a nucleic acid fragment or sequence of factor V or a mutation in Factor V gene that is correlative to APC-resistance and thrombosis is replete with unpredictable experimentation and is undue experimentation.

Appellant assert on page 11, last paragraph that the knowledge of a specific mutation in the Factor V gene is not required to practice the invention as recited in claim 54. Appellants state that the present application has conclusively established the association between Factor V and APC resistance based on extensive clinical and biochemical evidence. However, as stated above, the claims are drawn to a method of determining an individual's risk of APC resistance by determining a presence of a factor V mutation. The claims are not drawn to determining biochemical activity assay to determine the association of factor V with APC resistance. Furthermore, the specification disclose immunology assays to determine the activity of APC, which is not correlative to determining a mutation in the nucleic acid sequence of factor V gene and its association with APC resistance.

Appellants state that it would not be necessary to screen and analyze the factor V gene from hundreds of patients to identify any putative mutations within the gene to establish a relationship between mutations and recited phenotype, APC resistance. However, as described above, de Visser et al. teach APC resistance depends on the type of clotting test, particular reagent used, and the influence of other factors, apart from FVL that determine the APC resistance. De Visser et al. teach that the APC resistance assay reflect the ratio between the concentration of wild type FV molecule and the FV molecule in plasma and a mutation or allele associated with a reduced FV level results in an increased level of FV, leading to a more reduced normalized APC sensitivity ratio (see page 581, 2nd column, 1st paragraph). de Visser et al. teach that the mechanism which underlies the reduction of FV levels has to be further investigated (see page 581, 2nd column, 1st paragraph). de Visser demonstrates the unpredictability of determining a mutation in the Factor V gene and determining its association with an increased risk of thrombosis and APC resistance. De Visser demonstrate that APC resistance and reduction of factor V gene levels needs to be further investigated, which demonstrates the unpredictability of associating APC resistance to any factor V mutation. Therefore, a large study would be require to predictably correlate a mutation in the factor V gene and the risk in any type of individual (human, monkey, dog, etc) and APC resistance.

Appellants state on page 12-13, that the sequence of factor V gene was known, all methods needed to conduct nucleic acid assays were well known in the art when the application was filed and it was well within routine skill of an ordinary artisan to determine what sequence substitution would be silent or cause only conservative substitutions in the factor V gene. As stated above, although amino acid substitution, isolation, and amplification of nucleic acids are

routine assays the method of predictably correlating and determining a risk of thrombosis or APC-resistance by any mutation in Factor V gene is not a routine assay. As stated above, for one of skill in the art to predictably correlate any mutation in Factor V gene with the risk of developing thrombosis in an individual, as well as APC-resistance would require undue experimentation. The skilled artisan would have to perform an extremely large study and include different populations to determine if in fact there is an association with "any" mutation in Factor V gene and thrombosis and APC-resistance. The results of such a study are clearly unpredictably, as discussed in the rejection above.

Appellants on page 13, last two paragraphs, state that Shen et al. discuss in detail certain mutations in factor V gene that are silent or only cause conservative substitutions and that one of skill in the art would be able to readily isolate and amplify lymphocytes of an individual that had APC resistance phenotype or was at risk of APC resistance using methods and reagents described in Shen et al. Appellants stated that one of skill would readily have been able to determine the presence or absence of abnormal sequence in the individual's factor V gene by comparing the normal factor V sequence disclosed by Jenny et al. to determine whether a particular abnormal sequence was a mutation associated with APC resistance or silent mutation causing only conservative substitutions based on the teachings of Shen et al. It is noted that Shen et al. is post filing art. Shen et al was published in April 1993, while applicants' priority documents were filed in January 1993. Therefore, Shen et al. was not prior art and does not reflect the state of the prior art at the time the invention was filed. Furthermore, as stated above, de Visser et al. teach the unpredictability of associating APC activity assays and correlating these assays with mutation analysis. Therefore, one skilled in the art would not have been able to

make and use the claimed invention of determining a presence of a factor V mutation associated with APC resistance in an individual at risk for developing APC resistance, as biochemical assays disclose the unpredictability of associating APC resistance with factor V mutations.

Appellants assert that a particular mutation in the factor V gene that caused APC resistance was determined by a skilled artisan, based upon disclosure of the present application armed with the knowledge in the art without undue experimentation. Appellants assert that Voorberg et al. reported that a mutation at position Arg506 in factor V gene was responsible for thromboembolism associated with APC resistance based on the disclosure of the present invention and the knowledge available in the art. However, post filing art teach that the mutation of Arg 506, factor V leiden mutation, is not predictive of any type of thrombosis, as the claimed invention broadly encompasses. Bertina et al. teach that factor V Leiden mutation is a risk factor for deep-vein thrombosis, cerebral vein thrombosis, superficial vein thrombosis, and portal vein thrombosis but not for primary pulmonary embolism and retinal vein thrombosis. Additionally, Price et al. teach that Factor V Leiden mutation is associated with primary and recurrent venous thromboembolism but is not associated with an increase risk for arterial thrombosis (see data synthesis, page 895). Furthermore, Price et al. teach that no association was seen between factor V Leiden mutation and thromboembolism associated with surgery, trauma or cancer (see page 898, 1st paragraph, 1st column). Price et al. teach the largest study to address the association of risk of arterial thromboembolism and factor V Leiden mutation, no significant difference in the prevalence of the factor V mutation was found between men with myocardial infarction, cerebrovascular disease, and men without cardiovascular disease. Therefore, based on the teaching in the specification and the unpredictability of determining any

mutation and its association with any type of thrombosis in any individual as evidence by post filing art coupled with the lack of guidance in the specification and knowledge known in the art at the time of invention, the claimed invention required undue experimentation.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

This examiner's answer contains a new ground of rejection set forth in section **(9)** above. Accordingly, appellant must within **TWO MONTHS** from the date of this answer exercise one of the following two options to avoid *sua sponte* **dismissal of the appeal** as to the claims subject to the new ground of rejection:

(1) **Reopen prosecution.** Request that prosecution be reopened before the primary examiner by filing a reply under 37 CFR 1.111 with or without amendment, affidavit or other evidence. Any amendment, affidavit or other evidence must be relevant to the new grounds of rejection. A request that complies with 37 CFR 41.39(b)(1) will be entered and considered. Any request that prosecution be reopened will be treated as a request to withdraw the appeal.

(2) **Maintain appeal.** Request that the appeal be maintained by filing a reply brief as set forth in 37 CFR 41.41. Such a reply brief must address each new ground of rejection as set forth in 37 CFR 41.37(c)(1)(vii) and should be in compliance with the other requirements of 37 CFR 41.37(c). If a reply brief filed pursuant to 37 CFR 41.39(b)(2) is accompanied by any amendment, affidavit or other evidence, it shall be treated as a request that prosecution be reopened before the primary examiner under 37 CFR 41.39(b)(1).

Extensions of time under 37 CFR 1.136(a) are not applicable to the TWO MONTH time period set forth above. See 37 CFR 1.136(b) for extensions of time to reply for patent applications and 37 CFR 1.550(c) for extensions of time to reply for ex parte reexamination proceedings.

Respectfully submitted,
Sarae Beusch

**A Technology Center Director or designee must personally approve the new ground(s) of rejection set forth in section (9) above by signing below:**

George Elliqt
Director, TC1600

Conferees:

Jean Witz
QAS, TC1600

Ram Shukla
SPE, Conferee

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER